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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/599,460	09/28/2006	Yoko Yamagata	56861	9304

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EXAMINER	
BURKHART, MICHAEL D	

ART UNIT	PAPER NUMBER
1633	

MAIL DATE	DELIVERY MODE
03/29/2011	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/599,460	YAMAGATA ET AL.	
	Examiner	Art Unit	
	MICHAEL BURKHART	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 August 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,7-9,24 and 25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,7-9,24 and 25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8/13/2010 has been entered.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in Graham v. John Deere Co., 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1, 2, 7-9, 24 and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Elgersma et al (Neuron, 2002), Wang et al (PNAS, 2003), Hanson et al (Neuron, 1994) and

Sutoo et al (Brain Res., 2002). **This rejection is maintained for reasons made of record in the Office Actions dated 7/9/2009, 2/18/2010, 6/7/2010, and for reasons set forth below.**

Response to Arguments

Applicant's arguments filed 8/13/2010 have been fully considered but they are not persuasive. Applicants essentially assert that: 1) the prior art does not provide a predictable means for generating the claimed animals, nor healthy knock-in animals; 2) the K42M/R mutations of Hanson et al are only taught results in cell lines; 3) Wang et al teach an F89G mutation, outside the scope of the instant claims, and overexpression of this mutant only; 4) Elgersma et al do not teach an inactive CaMKIIalpha having a modified residue in the catalytic domain; 5) claim 2 recites unexpected results.

Regarding 1), these assertion are countered by the facts and results in the prior art, not only art cited in this rejection, but supplied by applicants themselves. Applicants appear to want a 35 USC 102 level of disclosure in the prior art whereas this is a 35 USC 103 rejection. There is always some unpredictability about the outcome of complex experiments, particularly those involving in vivo results such as this case. However, there is no technical burden to the creation of the mice (and cells) in the first place, nor in the assessment of the phenotype. Ample motivation to create the mice and cells has been provided and has not been disputed. Given the totality of the prior art teaching that CaMKIIalpha has a prominent role in neuronal activity and learning, it is not surprising that such a complex and broadly worded phenotype as "neuronal activity" is affected in certain areas of the brain but not others. Applicants provide a reference (Kirkwood et al) wherein CaMKIIalpha -/- mice are prepared, and such mice are viable. How

then could preparing mice that actually express the CaMKIIalpha protein, albeit harboring a substitution mutation, be unpredictable or difficult when mice that COMPLETELY LACK the protein can be prepared? Applicants are further directed to the results of Elgersma et al wherein mutant CaMKIIalpha knock-in mice are prepared and not associated with any difficulty in breeding. Applicants are inventing problems that do not exist or have been solved by the prior art. That the CaMKIIalpha knock-out mice may be difficult to breed does not mitigate against this rejection as these attempts were obviously successful, and knock-out mice (completely lacking the protein) are difficult to compare to knock-in mutations.

The concept and techniques for targeting literally any given gene for a knock-in mutation were known to the skilled artisan at least by the time of Elgersma et al (e.g. Mak et al, 2001 and Giese et al, 1998, of record), as was the sequence and structure of the CaMKIIα gene (see Colbran et al, 2004, of record, in particular, Fig. 1). Hanson et al describe precisely how to generate the substitution mutations (p. 953, second column, first full ¶). That the CaMKIIα gene may be large (applicants have not provided a copy of the Nishioka et al reference they rely upon, hence any teachings within have not been considered) is not disputed at the moment, but this does not set it apart from literally any other mammalian gene targeted for a knock-in mutation, as such genes also comprise various numbers of exons and introns. Applicants assertion is unsupported by any facts or reasoning and is contradicted by the successful gene targeting methods taught by the totality of the prior art.

Regarding 2), this assertion is false on its face, as it is not accompanied by any facts or scientific reasoning, in contrast to the results of Hanson et al (published in a peer-reviewed journal). Hanson et al teach that no modifications were made in the association domain of

CaMKIIalpha (Fig. 1a), thus, it is not clear why any negative effects would be expected on the ability of the mutant to multimerize, as this is the domain responsible. Further, it has been explained that the K42 mutants maintained the ability to multimerize with other CaMKII subunits/isoforms, which may number from 8-10 in the holoenzyme (Hanson et al, page 943, second column). This is all that is required to meet the claim limitation of "a capacity of multimerizing subunits are maintained" , there is no requirement that the claimed CaMKII protein form a "homomultimer" as applicants insist. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., forming "homomultimers") are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See In re Van Geuns, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Regarding 2) and 4), these assertions have been stipulated previously. Neither Wang, Hanson or Elgersma et al were relied upon to teach the claim limitations applicants are referring to.

Further regarding 2) - 4), in response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); In re Merck & Co., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Regarding 5), the claim is broadly worded such that only "neuronal activity" must be affected (not CaMKIIα expression, as applicants appear to argue), and this limitation is only

found in claim 2. Applicants appear to want a 35 USC 102 level of disclosure in the prior art whereas this is a 35 USC 103 rejection. There is always some unpredictability about the outcome of complex experiments, particularly those involving in vivo results such as this case. However, there is no technical burden to the creation of the mice (and cells) in the first place, nor in the assessment of the phenotype. Ample motivation to create the mice and cells has been provided and has not been disputed. Given the totality of the prior art teaching that CaMKIIα has a prominent role in neuronal activity and learning, it is not surprising that such a complex and broadly worded phenotype as "neuronal activity" is affected in certain areas of the brain but not others. The activity of CaMKIIα can be partially supplemented by CaMKIIβ (Giese et al, page 870, middle column). This may explain why differential effects are found in certain areas of the brain when the claimed mutants are used, or it could be that CaMKIIα is not required for the measured "neuronal activity" in the cerebral cortex and striatum even though it may be highly expressed in these regions. An example of an unexpected result from using the claimed mice would be that no affects on neuronal activity were found in any part of the CNS, as this would contradict the teachings of the prior art.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MICHAEL BURKHART whose telephone number is (571)272-2915. The examiner can normally be reached on M-F 8AM-5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michael Burkhart/
Primary Examiner, Art Unit 1633